Concerning the rejections under 35 U.S.C. §103(a)

A. The rejection of claims 75-77, 81-83, 88, 98, 100-101, 103-105, 107, 109-111, 118-132 and 136-146 as allegedly obvious over Qu or Hindley, in view of Langer and Leary, has been reiterated.

Applicants respectfully maintain their traversal of this rejection. As discussed with the Examiner in the November 12 telephone interview, the pending claims recite primers which are **covalently coupled** to a chromophore or fluorophore. If the biotin-labeled nucleotide of Langer were incorporated into a probe according to the method of Leary, one would obtain a mixed population of probes[1] covalently coupled to varying numbers of biotin molecules. As is known to those of skill in the art, biotin is neither a chromophore nor a fluorophore.

As admitted in the Office Action dated August 26, 1998 (paper No. 26, pages 4-5), Qu and Hindley each teach the use of a 5' end labeled DNA primer. The primer of Qu and Hindley is used for DNA sequencing and is end-labeled with a radioactive label. Thus, neither Qu nor Hindley disclose a primer covalently labeled with a chromophore or fluorophore; moreover, neither suggests primers covalently labeled with a chromophore or fluorophore. Inasmuch as the combination of Langer and Leary disclose labeling with biotin, which is neither a chromophore nor a fluorophore, Langer and Leary fail to cure the deficiency of the primary references.

Furthermore, Applicants urge that a *prima facie* case of obviousness has not been made because, among other reasons, (1) no motivation existed in the art to combine the cited references in the manner suggested by the Examiner; (2) the Examiner has failed to point to any such motivation; (3) the combination of cited references neither discloses nor suggests the claimed compositions; and (4) the references cannot be combined in the manner suggested by the Examiner, as would be apparent to one of skill in the art.

As discussed with the Examiner in the November 12 telephone interview, one of skill in the art would appreciate that it is impossible to apply the methods of Langer and Leary to the

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[1] Applicants note that the method of Leary generates probes, not a primer as claimed. *See infra.*

compositions of Qu and Hindley. Qu and Hindley use 5' end-labeled DNA primers (radioactively labeled) for chain termination DNA sequencing. However, the population of labeled molecules resulting from a nick translation reaction is not suitable for use as a primer in a chain termination DNA sequencing reaction. For one, they would not be capable of hybridizing to a specific region on a template to generate a nested set of primer extension products having a common labeled end, as would be required by the methods of Qu and Hindley. Second, none of the members of the population would contain a 5' end label, because, in the process of nick translation, label is incorporated during the extension phase of the reaction.

For these reasons, the technique of nick translation cannot be used to generate a primer, such as would be used in the methods of Qu or Hindley. (Similarly, the technique of nick translation is incapable of generating a primer as claimed.) Additional support for the foregoing statement comes from the fact that, although the technique of nick translation was known in the art at the publication dates of the Qu and Hindley references, neither uses the technique of nick translation to generate their primers, indicating that those of skill in the art were aware that nick translation could not be used to make a labeled primer. In fact, no references disclosing the preparation of labeled primers by nick translation exist, simply because it is impossible to prepare a primer by nick translation, as is recognized by those of skill in the art.

Thus, not only does the combination of references fail to disclose or suggest the claimed compositions; there is also no motivation in the art to combine Langer and Leary, on the one hand, with Qu and Hindley, on the other, since the technique of nick translation (Langer and Leary) cannot be used to make a labeled primer as disclosed by Qu and Hindley.

Applicants wish to address certain statements made in the preceding Office Action, in order to clarify the distinction between a primer and a probe. It was asserted that the pending product claims to primers read on the probes of the prior art, as disclosed in the cited references (Paper No. 29, page 3). It was further asserted that probes are commonly a homogeneous population of molecules sharing a common sequence, because probes are most often made from

a homogeneous population of cloned DNA (Paper No. 29, page 4). The Office Action then concluded that, since a probe population is uniform, it is implicitly capable of initiation of polymerization at a predetermined site (Paper No. 29, page 4).

Applicants assert that all of these statements are incorrect with respect to **probes produced by the nick translation method of the cited references**. Although a homogeneous population of cloned DNA may be used as starting material for generating a collection of nick translated probes[2], the process of nick translation necessarily results in production of a heterogeneous collection of labeled probe molecules. This is because, in the process of nick translation, the starting molecules are nicked randomly, then label is incorporated by polymerization initiated at the nicks. In addition, the extent of polymerization from each nick is variable. Therefore, even a homogeneous population of starting molecules will give rise to a heterogeneous collection of labeled molecules, representing different sub-sequences of the starting molecule. Moreover, the methods of Langer and Leary do not generate a nucleic acid that is covalently coupled to a chromophore or fluorophore (as recited in the claims); rather, they produce a heterogeneous collection of nucleic acids covalently coupled to biotin.

Accordingly, a population of probes generated by the cited nick translation method is not uniform and is therefore not capable of initiating polymerization at a predetermined site, as asserted by the Examiner and as would be required, for example, for DNA sequencing, polymerase chain reactions, and other types of primer extension reactions.

The Office Action states that the rejection is based on the reasoning that labels used in one species of nucleic acid can be used in any species of nucleic acid. In response, Applicants point out that the claims recite primers labeled with a chromophore or fluorophore so as to allow chain extension by a polymerase. Extendible primers, labeled with a chromophore or fluorophore, were neither disclosed nor suggested by the prior art.

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[2] However, the technique of nick translation does not require that the starting material be a homogeneous population.

In summary, Qu and Hindley fail to disclose or suggest primers covalently coupled to a chromophore or fluorophore, and Langer and Leary fail to cure this deficiency. There are two reasons why the combined disclosures of Langer and Leary fail to cure the deficiencies of the primary reference. First of all, Langer and Leary teach the synthesis of probes, not primers. Secondly, the probes taught by Langer and Leary are covalently coupled to biotin, which is neither a chromophore nor a fluorophore. Since it is impossible to use the technique of nick translation, as disclosed by Leary, to generate a 5' end labeled primer useful for chain termination DNA sequencing according to Qu and Hindley, the Leary reference is inappropriately combined with Qu and Hindley's disclosure of sequencing primers. For these reasons, Applicants continue to maintain that the claimed compositions are non-obvious over these references, and once again urge that this rejection be withdrawn.

B. Claims 75-77, 81-83, 88, 98, 100-101, 103-105, 107, 109-111, and 118-146 stand rejected over Qu or, in the alternative, Hindley, each in view of Smith *et al.*, U.S. Patent No. 5,118,800; issued on June 2, 1992. The Office Action asserts that the effective filing date of the '800 patent is December 20, 1983.

Applicants have addressed the deficiencies of the Qu and Hindley references, *supra*. With respect to the '800 patent, and without conceding the correctness of the Office's assertion of the priority date for an enabling disclosure in the '800 patent, Applicants will present evidence that the present invention was completed before December 20, 1983. Applicants' representatives are in the process of obtaining statements from the inventors to this effect, which will be presented to the Office in the form of a Declaration under 37 C.F.R. § 1.131.

C. Claims 75-77, 81-83, 88, 98, 100-101, 103-105, 107, 109-111, and 118-146 stand rejected as allegedly obvious over Qu or Hindley, in view of Levinson *et al*, for reasons of record.

Applicants respectfully traverse this rejection. As set forth in the previous Response, dated February 26, 1999[3], the method of Levinson requires that the DNA to be labeled be partially depurinated, since Levinson's label reacts with the products of depurination. A careful review of Levinson indicates that only half of the depurinated sites react with Levinson's acriflavin label. Thus, any DNA labeled by Levinson's method will contain two types of regions that are incapable of base-pairing: (1) depurinated sites that have not reacted with acriflavin and (2) sites containing an acriflavin molecule in place of a purine base. As a consequence, the ability of a DNA molecule, labeled by Levinson's method, to hybridize to a unique sequence will be reduced and thus its ability to serve as a primer will be compromised. Thus, probes labeled according to Levinson could not have been used as sequencing primers in the methods of Qu or Hindley, leading to the conclusion that no motivation exists in the art to combine the disclosure of Levinson with those of Qu and Hindley; further suggesting that a *prima facie* case of obviousness has not been made. Furthermore, Levinson is totally silent as to whether DNA labeled by his method is extendible by a polymerase, as are the claimed primers.

From the comments presented in the previous Office Action (page 6) it is not clear whether the Examiner is relying on Levinson solely for his disclosure of a fluorescent label or also for his disclosure of a labeling method. Clearly Levinson's labeling method would have been ineffective to generate the end-labeled sequencing primers of Qu and Hindley, and would be ineffective to generate the claimed primers for the reasons stated above[4] and, in addition, because Levinson's method would result in different oligonucleotides having different numbers of labels[5], depending on their purine content. On the other hand, if the Office is suggesting that the label disclosed by Levinson could have been combined with art-recognized labeling methods to make the presently-claimed compositions obvious, the Office Action has failed to set forth

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[3] And also admitted in the Office Action dated August 26, 1998

[4] And for the reasons of record; see the previous Response dated February 26, 1999.

[5] And, hence, different relative mobilities.

how acriflavin, as disclosed by Levinson, could be combined with some labeling method other than Levinson's to generate a tagged, extendible primer, as claimed. Accordingly, a *prima facie* case of obviousness has not been made.

Since the cited combination of Qu's or Hindley's primers with Levinson's labeling method would not generate the claimed tagged, extendible primers, Applicants urge that this rejection be withdrawn.

CONCLUSION

Applicants have, by way of the amendments and remarks presented herein, made a sincere effort to overcome rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and/or the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 243132000105. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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